REMARKS

This Amendment B is submitted responsive to the Office Action mailed Sept. 24, 2009. Applicants respectfully request that these amendments and remarks be entered, and that the application so amended be reconsidered and allowed.

The Status of the Claims

Claims 1-5, 12-16, 18-20, 22-24, and 29-34 were pending as of issuance of the Sept. 24th Office Action.

Claims 1-5, 12-16, 18-20, 22-24, and 29-31 stand rejected under 35 U.S.C. § 112, 1st ¶ as allegedly failing to comply with the written description requirement.

Claims 1-5, 12-16, 18-20, and 22 stand rejected under 35 U.S.C. § 112, 2nd ¶ for alleged omitted essential steps.

Claims 1-5, 12, 22-24, and 31 stand rejected under 35 U.S.C. § 102(a) as being allegedly anticipated by Song et al., "Multislice Double Inversion Pulse Sequence for Efficient Black-Blood MRI", Magnetic Resonance in Medicine, vol. 47 pages 616-20 (2002) (hereinafter "Song").

Note: Office Action page 4 recites the rejection as under § 102(b); however, based on the comment at Office Action page 9 Applicants understand the § 102 rejections based on Song to be under § 102(a). Also, Applicants note that claims 25-28 were canceled in previous Amendment A, but are erroneously listed as rejected under § 102 at least at Office Action page 4 (listing claim 27) and page 7 (listing claims 25-27).

Claims 13-16, 18-20, 29, and 30 are indicated as containing allowable subject matter.

Claims 32-34 are allowed.

The § 112 rejections are remediated

The § 112 rejections were issued responsive to Applicants' amendment of the preamble of claims 1 and 23 reciting "to determine changes in microvascular blood

volume without the use of exogenous contrast or endogenous paramagnetic contrast using the parenchymal tissue signal" (claim 1) and "configured to determine changes in microvascular blood volume without the use of exogenous contrast or endogenous paramagnetic contrast using the parenchymal tissue signal" (claim 23). These recitations are deleted in this Amendment B.

Applicants note that the preambles were not given patentable weight (Office Action pages 3-4). Accordingly, the deletion of these preamble recitations does not affect the scope of the claims as examined.

These amendments obviate the § 112, 1st ¶ rejection since the subject matter alleged to be new matter is removed. These amendments also obviate the § 112, 2nd ¶ rejections since the rejected claims do not recite determining *changes* in microvascular blood volume and hence no "essential step" is imposed by the amended preamble.

Accordingly, Applicants respectfully request that the § 112 rejections be reconsidered and withdrawn.

The Claims Present Patentable Subject Matter and Should Be Allowed

Claims 32-34 are allowed.

Claim 23 is amended to incorporate the allowable subject matter of claim 29 and of claim 30 as a Markush group. As each of claims 29 and 30 are separately allowable, it is respectfully submitted that claim 23 which recites a Markush group of the allowable subject matter of claim 29 and of claim 30 is also allowable.

Claim 2 has been placed into independent form and has been further amended to recite wherein the performing of a blood signal-reduction magnetic resonance sequence includes performing a spatially non-selective inversion recovery magnetic resonance excitation sequence having an inversion time to substantially reduce the magnetic resonance signal from blood. The amendment finds support in the original specification at least by spatially non-selective inversion pulses (74, 74') and at page 7 lines 21-24; page 8 lines 34-36.

Song performs blood nulling using at least two inversion pulses – a non-selective pulse followed by a slice-selective inversion pulse. This constitutes a slice-selective inversion recovery preparation for blood nulling, whereas, the blood nulling approach of the present application is spatially nonselective. Amended claim 2 expressly recites this distinction over Song.

To illustrate, Song Fig. 1 is reproduced below:

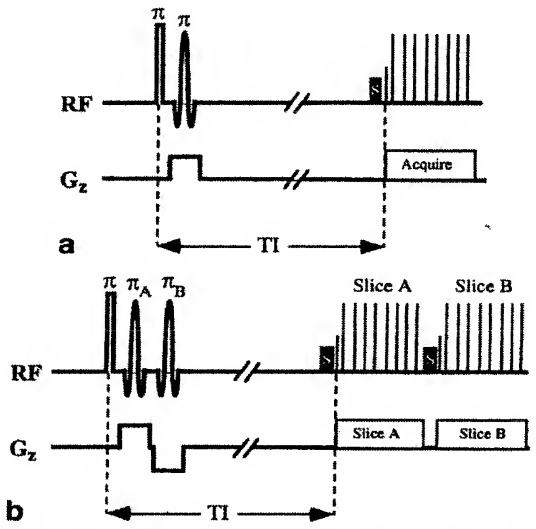

FIG. 1. Conventional (a) and modified dual-slice (b) double inversion FSE sequences. Boxes on the z-gradient axes (Acquire, Slice A, and Slice B) represent the gradient waveforms during the echo-train readouts. Pulses labeled "S" are for optional saturation of a chemical species.

Song Fig. 1 shows both the conventional slice-selective double-inversion blood nulling technique comprising two RF inversions π of Fig. 1(a), and the improved (modified) slice-selection so-called double-inversion technique of Song Fig. 1(b) comprising three RF inversions π, π_A, π_B. In both cases, the first inversion pulse π is spatially nonselective, as seen by the lack of any corresponding G_z gradient field applied at the time of the first excitation π, while the second (and third, in Fig. 1(b)) inversion is spatially selective due to concurrent application of a G_z gradient field.

The use of a *slice-selective* inversion recovery preparation (π, π) (Fig. 1(a)) or (π, π_A, π_B) (Fig. 1(b)) is taught by Song to be critical to the black-blood technique of Song. In the black-blood technique, the inversion sequence is assumed to null *all* signal (both blood and tissue), *except* in one selected slice. As explained by Song:

> The net effect of the two pulses is the inversion of the spins outside the desired slice, while those in the slice are unaffected. Inverted blood then flows into the imaging slice, replacing unaffected blood. Data are acquired after a period TI following the initial inversion, typically using fast spin echo (FSE or RARE) or spiral readouts. TI is set to a value at which the recovering inverted blood reaches a null signal and is therefore T_1-dependent.
>
> Song page 616 text crossing from left-to-right column.

The technique is "black blood" because the signal from the imaged slice is not nulled, *except* for the blood, which is blood that flows into the imaged slice during the inversion recovery time TI and is nulled at time TI. Thus, the imaged slice has signal from the stationary tissue, but not from the nulled blood flowed into the slice during the imaging. The blood is nulled (i.e., appears black in the image since there is no blood signal), and so the vessel lumen is accurately depicted in black, allowing the vessel wall to be assessed. *See* Song page 616 first column.

In sum, Song teaches nulling *both* the blood and tissue signals *except* in a selected slice where all non-blood signal remains. The use of such a *slice-selective* nulling in Song enables the black blood imaging technique to work. Song's black blood imaging technique would not work with a spatially non-selective inversion recovery sequence. Rather, for the method of Song to work at least two inversion pulses are needed in the preparation, one non-selective and another slice selective.

The method of claim 2 operates in a fundamentally different manner. The illustrative pulse sequence of present application Fig. 2 is reproduced below:

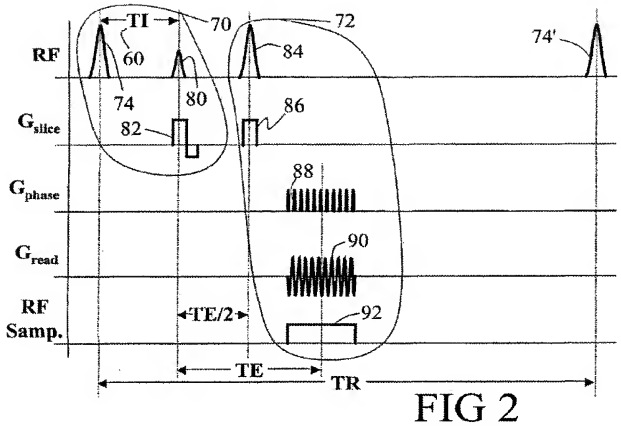

FIG 2

The inversion pulse (74) is spatially nonselective, as shown by the lack of any concurrently applied magnetic field gradient field. (Note that the excitation pulse (80) is not part of the inversion sequence, but rather is the excitation pulse (80) of the imaging sequence performed *after* the inversion recovery time TI has elapsed. *See* present application page 7 lines 25-29.)

As recited in claim 2, the blood signal-reduction magnetic resonance excitation sequence substantially reduces a magnetic resonance signal from blood *while substantially retaining parenchymal tissue signal.* Song, on the other hand, assumes its inversion recovery sequence will null both blood and tissue signal outside the slice of interest.

The approach of the present application employs a TI selected to precisely null the *blood* signal while substantially *retaining* parenchymal tissue signal. As explained in the present application:

> Because the blood is in a null condition at the time the excitation pulse 80 is applied, negligible magnetic resonance signal is excited in the nulled blood by the excitation pulse 80. Tissue such as fat, gray and white brain tissues, and the like generally have a different T1 value from that of blood, and so these tissues are not at a null condition at the time the excitation pulse 80 is applied. Hence, the excitation pulse 80 excites magnetic resonance predominantly in tissue.
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> Present application page 7 lines 29-34.

Because the method of claim 2 employs a blood signal-reduction magnetic resonance excitation sequence that substantially reduces a magnetic resonance signal from blood

while substantially retaining all parenchymal tissue signal (not just in a slice of interest), there is no need for the sequence to be spatially selective. Indeed, the blood signal reduction sequence is preferably spatially *non*-selective:

> Preferably, the inversion pulse 74 is not accompanied by a spatial encoding magnetic field gradient pulse or is accompanied by a relatively small spatial encoding magnetic field gradient pulse. This ensures that the spins of blood throughout the subject region of interest reach the null condition after the inversion time delay TI 60. In particular, the blood nulling is independent of blood flow since the blood-nulling inversion pulse 74 is spatially non-selective or selects a relatively large region. Thus, flowing blood that flows into the slice of interest at the time of excitation or at the time of readout is nulled appropriately.
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> Present application page 7 lines 18-24.

Claims 3-5 are amended for consistency with amended claim 2. The amendment to claim 5 finds specific support at least at least at page 8 lines 34-36 and spatially non-selective inversion pulse (74').

In view of the foregoing, it is respectfully submitted that claims 2-5 present patentable subject matter. As the § 112 rejections are also remediated herein, Applicants earnestly request reconsideration and allowance of claims 2-5.

Claim 1 recites performing a blood signal-reduction magnetic resonance excitation sequence that substantially reduces a magnetic resonance signal from blood *while substantially retaining parenchymal tissue signal*; subsequent to the performing of the blood signal-reduction magnetic resonance excitation sequence, performing a readout magnetic resonance sequence to acquire a magnetic resonance signal arising predominantly from parenchymal tissue; and determining a microvascular blood volume parameter *based on the acquired magnetic resonance signal arising predominantly from parenchymal tissue*.

In contrast, the black blood imaging approach of Song performs a blood *and tissue* signal-reduction magnetic resonance excitation sequence (π, π) or (π, π_A, π_B) that

substantially reduces a magnetic resonance signal from *both* blood *and tissue except for a single slice of interest*.

Song does disclose performing a subsequent readout magnetic resonance sequence to acquire a magnetic resonance signal arising predominantly from remaining tissue in a single slice. However, this is achieved by the slice-selective nulling sequence of Song, rather than by employing a *blood* signal-reduction magnetic resonance excitation sequence that substantially reduces a magnetic resonance signal from blood *while substantially retaining parenchymal tissue signal*, as recited in claim 1.

Still further, Song does not disclose or fairly suggest determining a microvascular blood volume parameter *based* on the acquired magnetic resonance signal arising predominantly from parenchymal tissue. The closest that Song comes to this limitation is disclosure of "delineation of the boundary separating the [blood vessel] lumen from the vascular wall, which is crucial for measuring wall thickness and plaque morphology." Song page 616 left column. In principle, one could compute a *macro*vascular blood volume per unit vessel length based on the measured vessel lumen. However, *Song does not disclose or fairly suggest such a computation*. Moreover, the vessels of interest for imaging in Song are the major arteries and/or veins (i.e., the *macro*vasculature), which do not contribute to the *microvascular* blood volume.

Claim 2, in contrast, recites determining a *microvascular* blood volume parameter based on the acquired magnetic resonance signal arising predominantly from parenchymal tissue. Song does not disclose or fairly suggest this operation.

The Office Action indicates that each of **claims 13-16 and 18-20** that depend directly or indirectly from claim 1 contain allowable subject matter. Thus, these claims present further bases for patentability beyond those recited in base claim 1.

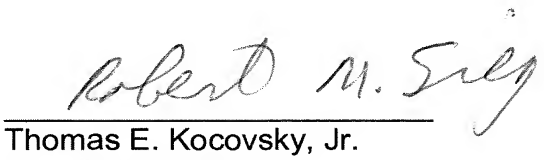
In view of the foregoing, it is respectfully submitted that claims 1, 12-16, and 18-20 present patentable subject matter. As the § 112 rejections are also remediated herein, Applicants earnestly request reconsideration and allowance of these claims.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that claims 1-5, 12-16, 18-20, 22-24, and 29-34 (all claims) are in condition for allowance, and earnestly request reconsideration and allowance of claims 1-5, 12-16, 18-20, 22-24, and 29-34 (all claims).

Respectfully submitted,

FAY, SHARPE LLP



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